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REMARKS

Reconsideration is requested.

Claims 1-13, 15, 23-36, 38-39 and 41-56 have been canceled, without prejudice.

Claims 14, 16-22, 37 and 40 are pending. Claims 57-69 have been added. Support for the amended claims may be found throughout the specification, as further described below. No new matter has been added. Upon entry of the present amendment, claims 14, 16-22, 37, 40 and 57-69 will be pending.

The applicants acknowledge, with appreciation, the Examiner interview of December 5, 2003. The Interview Summary is an a brief and accurate summary of the issues discussed during the interview.

The following is submitted in response to the clarification of the indicated items requested by the Examiners during the interview.

The constructs of the Examples of the present specification contain a sequence encoding the amino acids encoded by MGF exons 3/4/5/6, i.e. the amino acid sequence of Figure 5 or SEQ ID NO: 2. As noted on page 9 of the specification, Figures 6 and 7 (i.e., SEQ ID NOs: 4 and 6) also describe amino acid sequences of MGF exons 3/4/5/6. Thus, the sequence encoded by the construct is a preferred embodiment discussed at page 10, lines 4-5 of the specification. The Examiner is urged to appreciate however that the specification also describes that proteins of the invention include sequences having the 4-5-6 exon structure. See, page 9, lines 17-19 and page 11, lines 15-17, for example. The specification describes the present invention as including MGF, which is

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any IGF-I splice variant that includes the characteristic 4-5-6 exon pattern as opposed to the 5/6 exon pattern of regular liver-type IGF-I. The claims have been amended to recite these two embodiments of the disclosed invention, without prejudice, to advance prosecution. The recited percent identities are described, for example, at page 12, lines 4-5 of the specification.

The specification has been amended above to include sequence identifiers for the sequences of the figures. Support for the amendments may be found throughout the specification. Specifically, page 9, lines 16-23 discloses that Figures 5, 6 and 7 describe SEQ ID NOs: 1-6 and that Figures 8, 9 and 10 describe SEQ ID NOs: 9-14. See, also page 10, lines 15-23 of the specification.

Moreover, one of ordinary skill in the art will appreciate from page 9 and the entirety of the specification that Figure 11 is a comparison of the amino acid sequences of human, rat and rabbit MGF and human, rat and rabbit IGF-1 and that Figure 11 describes exons 4-6, as compared to Figures 5-9 (i.e., SEQ ID NOs: 2, 4, 6 (MGF) and 9, 10, 12 and 14 (IGF-I)) which also describe Exon 3. In each sequence in Figure 11, the first amino acid is amino acid 26 (Asn) in the corresponding sequence in Figures 5-9 and SEQ ID NOs: 1-14. Figure 11 therefore describes the following: Hu MGF: Amino Acid No. 1 = Amino Acid No. 26 of SEQ ID NO: 2 and Figure 5; Rat MGF: Amino Acid No. 1 = Amino Acid No. 26 in SEQ ID NO: 4 and Figure 6; Rab MGF: Amino Acid No. 1 = Amino Acid No. 26 in SEQ ID NO: 6 and Figure 7; Hu IGF: Amino Acid No. 1 = Amino Acid No. 26 in SEQ ID NO: 10 and Figure 8; Rat IGF: Amino Acid No. 1 = Amino Acid No. 26 in SEQ ID NO: 12 and Figure 9; Rab IGF: Amino Acid No. 1 = Amino Acid No.

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26 In SEQ ID NO: 14 and Figure 10. The specification has been amended to include this specific disclosure.

As for the recitation of percent identity, the specification describes on page 12, for example, the recited values. Moreover, as requested by the Examiners during the interview, the applicants note the following with regard to the sequences of the Figures and their similarity.

There are fairly few differences between the human, rat and rabbit exon 3/4/5/6 MGF sequences, and similarly there are fairly few differences between the human, rat and rabbit exon 4/5/6 MGF sequences. However, the identity between some pairs of the three sequences is less than 90%, the lowest being for human/rat at 82.6% by the calculations further described below. The above recited 80% or greater and 90% or greater sequence identity therefore is believed to also be supported by the examples of the present specification.

The Examiner is requested to consider the following sequence alignment and discussion in this regard.

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Sequence SEQ ID NO: 2 (Human, Figure 5) 3-4-5-6

Sequence SEQ ID NO: 4 (Rat, Figure 6) 3-4-5-6

Sequence SEQ ID NO: 6 (Rabbit, Figure 7) 3-4-5-6

Hu	Gly	Pro	Glu	Thr	Leu	Cys	Gly	Ala	Glu	Leu	Val	Asp	Ala	Leu	Gln	Phe
Rat	Gly	Pro	Glu	Thr	Leu	Cys	Gly	Ala	Glu	Leu	Val	Asp	Ala	Leu	Gln	Phe
Rab	Gly	Pro	Glu	Thr	Leu	Cys	Gly	Ala	Glu	Leu	Val	Asp	Ala	Leu	Gln	Phe
	1	.	5						10					15		

Hu Val Cys Gly	Asp	Arg Gly Phe Tyr Phe Asn Lys Pro Thr	Gly	Tyr Gly
Rat Val Cys Gly	Pro	Arg Gly Phe Tyr Phe Asn Lys Pro Thr	Vai	Tyr Gly
Rab Val Cys Gly	Asp	Arg Gly Phe Tyr Phe Asn Lys Pro Thr	Gly	Tyr Gly
	20		25	30

Hu	Ser	Ser	Ser	Arg	Arg	Ala	Pro	Gln	Thr	Gly	Ile	Val	Asp	Glu	Cys	Cys
Rat	Ser	Ser	Ile	Arg	Arg	Ala	Pro	Gln	Thr	Gly	Ile	Val	Asp	Glu	Cys	Cys
Rab	Ser	Ser	Ser	Arg	Arg	Ala	Pro	Gln	Thr	Gly	Ile	Val	Asp	Glu	Cys	Cys
			35				40						45			

Hu	Phe	Arg	Ser	Cys	Asp	Leu	Arg	Arg	Leu	Glu	Met	Tyr	Cys	Ala	Pro	Leu
Rat	Phe	Arg	Ser	Cys	Asp	Leu	Arg	Arg	Leu	Glu	Met	Tyr	Cys	Val	Arg	Cys
Rab	Phe	Arg	Ser	Cys	Asp	Leu	Arg	Arg	Leu	Glu	Met	Tyr	Cys	Ala	Pro	Leu

Hu	Lys	Pro	Ala	Lys	Ser	Ala	Arg	Ser	Val	Arg	Ala	Gln	Arg	His	Thr	Asp
Rat	Lys	Pro	Thr	Lys	Ser	Ala	Arg	Ser	Ile	Arg	Ala	Gln	Arg	His	Thr	Asp
Rab	Lys	Pro	Ala	Lys	Ala	Ala	Arg	Ser	Val	Arg	Ala	Gln	Arg	His	Thr	Asp

Hu	Met	Pro	Lys	Thr	Gln	Lys	Tyr	Gln	Pro	Pro	Ser	Thr	Asn	Lys	Asn	Thr
Rat	Met	Pro	Lys	Thr	Gln	Lys	Ser	Gln	Pro	Leu	Ser	Thr	His	Lys	Lys	Arg
Rab	Met	Pro	Lys	Thr	Gln	Lys	Tyr	Gln	Pro	Pro	Ser	Thr	Asn	Lys	Lys	Met
										85		90			95	

Hu	Lys	Ser	Gln		Arg	Arg	Lys	Gly	Ser	Thr	Phe	Glu	Glu	His	Lys
Rat	Lys	Leu	Gln	Arg	Arg	Arg	Lys	Gly	Ser	Thr	Leu	Glu	Glu	His	Lys
Rab	Lys	Ser	Gln	Arg	Arg	Arg	Lys	Gly	Ser	Thr	Phe	Glu	Glu	His	Lys

Comparisons:

Exons 4-5-6

Human/Rat: $1 - (15/86) = 82.6\%$

Human/Rabbit: 1-(4/86) = 95.4%

Rat/Rabbit: 1-(14/86) = 83.7%

Exons 3-4-5-6

Human/Rat: $1 - (16/111) = 85.6\%$

Human/Rabbit: 1-(4/111) = 96.4%

Rat/Rabbit: 1-(15/111) = 86.5%

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For exons 4-6, for example, the similarity can be seen graphically in the Figure 11 comparison. Specifically, SEQ ID NO: 2 (Human MGF) is 110 amino acids long, while SEQ ID NOs: 4 and 6 (Rat/Rabbit) have 111 amino acids. See, Figure 11 (final group of lines) for the location of the gap in human MGF. If, for example, these three sequences are lined up in the manner of Figure 11 but also including exon 3 in each case (cf. Figures 5-7), as a measure of sequence identity, there are the following 15 differences between human and rat: (i-ii) Gly/Val and Ser/Ile at Figure 11, first group of lines, positions 5 and 10, (iii-vii) Ala/Val, Pro/Arg, Leu/Cys, Ala/Thr and Val/Ile at Figure 11, second group of lines, positions 13-15, 18 and 24, (viii-xii) Tyr/Ser, Pro/Leu, Asn/His, Asn/Lys, Thr/Arg at Figure 11, third group of lines, positions 14, 17, 20, 22 and 23, (xiii) Ser/Leu at Figure 11, fourth group of lines, position 1, (xiv) Gap in Human MGF at Figure 11, fourth group of lines, position 3, and (xv) Phe/Leu at Figure 11, third group of lines, position 10. Moreover, there are the following four (4) differences between human and rabbit: (i) Ser/Ala at Figure 11, second group of lines, position 20, (ii-iii) Asn/Lys, Thr/Met at Figure 11, third group of lines, positions 22 and 23, and (iv) Gap in Human MGF at Figure 11, fourth group of lines, position 3. Finally, there are the following 14 differences between rat and rabbit: (i-ii) Val/Gly and Ile/Ser at Figure 11, first group of lines, position 10, (iii-viii) Val/Ala, Arg/Pro, Cys/Leu, Thr/Ala, Ser/Ala and Ile/Val at Figure 11, second group of lines, positions 13-15, 18, 20 and 24, (ix-xii) Ser/Tyr, Leu/Pro, His/Asn, Arg/Met at Figure 11, third group of lines, positions 14,

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17, 20 and 23), (xiii) Leu/Ser at Figure 11, fourth group of lines, position 1, (xiv) Leu/Phe at Figure 11, fourth group of lines, position 10.

Accordingly, the sequence similarity or identity over the sequence of exons 4-6, as a measure of sequence similarity, is as follows: human/rat = 82.6% (i.e., 1 - 15/86); human/rabbit = 95.4% (i.e., 1 - 4/86); rat/rabbit = 83.7% (i.e., 1 - 14/86). The compared sequences of exons 4-6 of the specification have 86 amino acids, where the gap in the human sequence is being counted, in this example, as both a difference and a placeholder.

In exon 3, there is one (1) further difference between human and rat ((xvi) Compare Figure 5 (human), amino acid sequence position 20, Asp, with Figure 6 (rat), amino acid sequence position 20, Pro); no further differences between human and rabbit; and one (1) further difference between rat and rabbit ((xv) Compare Figure 6 (rat), amino acid sequence position 20, Pro with Figure 7 (rabbit), amino acid sequence position 20, Asp).

Thus, in the exon 3-6 sequences of SEQ ID NOS: 2, 4 and 6, there are a total of: 16 differences between human and rat; 4 differences between human and rabbit; and 15 differences between rat and rabbit. Taking the 111 amino acid length of the compared sequences across exons 3-6, this gives $16/111 \times 100 = 14.4\%$ difference, or 85.6% identity between human and rat; $4/111 \times 100 = 3.6\%$ difference, or 96.4% identity between human and rabbit; and $15/111 \times 100 = 13.2\%$ difference, or 86.5% identity between rat and rabbit.

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The claims are submitted to be supported by an enabling disclosure which adequately describes the claimed invention.

Reconsideration and withdrawal of the Section 112, first paragraph, rejection of claims 14-56 stated in ¶6 of the Office Action dated July 2, 2003 (Paper No. 18) is requested in view of the above and arguments of record.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is invited to contact the undersigned in the event anything further is required to place the application in condition for allowance.

Respectfully submitted,

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